Statistics
in Medicine

1. Derivation of $\xi_q\left(Y_{ij}^{a,\Psi_p\left(M_{ij}^{a^*}|C_{ij}=c,b_{0i},g_{0i}\right)}|\ C_{ij}=c,b_{0i},g_{0i}\right)$

The q^{th} percentile of the potential outcome Y_{ij} distribution setting $A_{ij}=a$ and $M_{ij}=\Psi_p(M_{ij}^{a^*})$ conditioning on the random intercepts is equal to:

$= \xi_q\left(Y_{ij}^{a,\Psi_p\left(M_{ij}^{a^*}|C_{ij}=c,b_{0i},g_{0i}\right)}|\ C_{ij}=c,b_{0i},g_{0i}\right)$

$= \int \xi_q\left(Y_{ij}^{a,\varphi}|\ C_{ij}=c,b_{0i},g_{0i},\Psi_p(M_{ij}^{a^*}|C_{ij}=c,b_{0i},g_{0i})=\varphi\right) dP_{\Psi_p\left(M_{ij}^{a^*}|C_{ij}=c,b_{0i},g_{0i}\right)}(\varphi)$ (Law of iterated expectations)

$= \int \xi_q\left(Y_{ij}^{a,\varphi}|\ C_{ij}=c,b_{0i},g_{0i}\right)\ dP_{\Psi_p\left(M_{ij}^{a^*}|C_{ij}=c,b_{0i},g_{0i}\right)}(\varphi)$ (Assumption 4)

$= \int \zeta_q(Y_{ij}|\ C_{ij}=c,b_{0i},g_{0i},M_{ij}=\varphi,A_{ij}=a)\ dP_{\psi_p(M_{ij}|C_{ij}=c,b_{0i},g_{0i},AP_{ij}=a^*)}(\varphi)$ (Assumptions 1 to 3)

$= \int[\gamma_0+g_{0i}+\gamma_1\ a+\gamma_2\ \varphi+\gamma_3\ a\ \varphi+\gamma_c^T c]\ dP_{\psi_p(M_{ij}|C_{ij}=c,b_{0i},g_{0i},AP_{ij}=a^*)}(\varphi)$

$= \gamma_0+g_{0i}+\gamma_1\ a+(\gamma_2+\gamma_3\ a)\int \varphi\ dP_{\psi_p(M_{ij}|C_{ij}=c,b_{0i},g_{0i},AP_{ij}=a^*)}(\varphi)+\gamma_c^T c$

$= \gamma_0+g_{0i}+\gamma_1\ a+(\gamma_2+\gamma_3\ a)\ (\beta_0+b_{0i}+\beta_1\ a^*+\beta_c^T\ c)+\gamma_c^T c$

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2. R code

```
install.packages(”rqpd”,repos=”http://R-Forge.R-project.org”)
library(rqpd)

mediation<-function(dataset,pollutant,methylation,protein) {
pol<-pollutant
dataset$pol2<-(pol-summary(pol)[4])/sqrt(var(pol,na.rm=TRUE))
dna<-methylation
dataset$dna2<-(dna-summary(dna)[4])/sqrt(var(dna,na.rm=TRUE))
outcome<-protein
dataset$outcome2<-(outcome-summary(outcome)[4])/sqrt(var(outcome, na.rm=TRUE))

mod<-rqpd(dna2 pol2+TMPCMA28+RHUMMA28+COS+SIN+AGE+BMI+as.factor(SMK2)
+DIABETE+STATIN NEUT+LYMPH+MONO+BASO+BATCH | ID, data=dataset,
panel(taus=c(0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9), lambda=0,tauw=rep(1/9,9)))

res<-matrix(ncol=9,nrow=1)
for(i in 1:9){res[1,i]<-mod$coefficients[17*(i-1)+1]}

mod2<-rqpd(outcome2 dna2+pol2+TMPCMA28+RHUMMA28+COS+SIN+AGE+BMI+as.factor(SMK2)
+DIABETE+STATIN+NEUT+LYMPH+MONO+BASO+BATCH | ID, data=dataset,
panel(taus=c(0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9), lambda=0,tauw=rep(1/9,9)))

res2<-matrix(ncol=9,nrow=1)
for(i in 1:9){res2[1,i]<-mod2$coefficients[18*(i-1)+1]}
res3<-matrix(ncol=9,nrow=1)
for(i in 1:9){res3[1,i]<-mod2$coefficients[18*(i-1)+2]}

  result<-rbind(res,res2,res3)
return(result) }

mediation.bootstrap<-function(dataset,pollutant,methylation,protein,n,npol,nmeth,nprot){
beta1<-matrix(nrow=n,ncol=9)
gamma2<-matrix(nrow=n,ncol=9)
gamma1<-matrix(nrow=n,ncol=9)
for (i in 1:n){
list<-dataset$ID[!duplicated(dataset$ID)]
a<-sample(list,replace=TRUE,size=777)
a<-a[order(a)]
data.set<-subset(dataset,ID %in% a[1])
for(k in 2:length(a)){ z<-subset(dataset,ID data.set<-rbind(data.set,z)}
temp<-mediation(data.set,data.set[,npol],data.set[,nmeth],data.set[,nprot])
beta1[i,]<-temp[1,]
gamma2[i,]<-temp[2,]
```



```
gamma1[i,]<-temp[3,]
print(i) }
return(cbind(beta1,gamma2,gamma1)) }

estimate.pn.ifn.fib<-mediation(try,try$PNMA28,try$IFNMEAN,try$FIB)
final.pn.ifn.fib<-mediation.bootstrap(try,try$PNMA28,try$IFNMEAN,try$FIB,1000,185,50,11)
```

3. Simulation study

3.1. Description of simulated cross-sectional data

We first consider a completely randomized binary exposure A_i (i=1, ..., N, where N=9,000) and simulate individual normally distributed potential outcomes $M_i^{a=0}$ (i.e., mediator variable under no treatment). We constructed the individual potential outcomes $M_i^{a=1}$ such that specific-deciles of the $M_i^{a=1}$ distribution were shifted from $M_i^{a=0}$ by different effect sizes (i.e., $\beta_{1,p}$). We then constructed M_i^{obs} based on the binary exposure such that, for each unit i, M_i^{obs} = [A_i $M_i^{a=1}$ + (1-A_i) $M_i^{a=0}$]. Finally, we constructed Y_i^{obs} such that specific deciles of the Y_i^{obs} distribution were shifted by $M_i^{obs} * \gamma_{2,q}$. These shifts were constant within decile of mediator and outcome observations. For simplicity, we construct the simulation without considering covariates.

We set up a simulation study contrasting scenarios for which the effects are only present at the extreme quantiles (scenarios 1 and 2) vs. a scenario for which the effects are present for a larger portion of the population sample (scenario 3). In scenario 1, the effects are only present at the extreme quantiles: above the 90^{th} quantile of the mediator and above the 90^{th} quantile of the outcome. This means, using the above notations, $\beta_{1,p} = \gamma_{2,q} = 0$ for each p and q, except for $p, q \geq 90$, that is, $\beta_{1,90} = \gamma_{2,90} = 10$.

True quantile mediated effects $\beta_{1,p}\gamma_{2,q}$									
Scenario 1									
p \ q	10	20	30	40	50	60	70	80	90
10	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	100

In scenario 2, the effects are present at the 80^{th} quantile and above for both the mediator and outcome. That is, $\beta_{1,p} = \gamma_{2,q} = 0$ for each p and q, except for $p, q \geq 80$, that is, $\beta_{1,80} = \gamma_{2,80} = 5$, that is, $\beta_{1,90} = \gamma_{2,90} = 10$.

True quantile mediated effects $\beta_{1,p}\gamma_{2,q}$									
Scenario 2									
p \ q	10	20	30	40	50	60	70	80	90
10	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	25	50
90	0	0	0	0	0	0	0	50	100

In scenario 3, the effects are present for a larger portion of the sample, i.e., at the 60^{th} percentile and above for the mediator and the outcome. That is, $\beta_{1,p} = \gamma_{2,q} = 0$ for each p and q, except for $p, q \geq 60$, for which, $\beta_{1,60} = \gamma_{2,60} = 2.5$, $\beta_{1,70} = \gamma_{2,70} = 5$, $\beta_{1,80} = \gamma_{2,80} = 7.5$, and $\beta_{1,90} = \gamma_{2,90} = 10$.

True quantile mediated effects $\beta_{1,p}\gamma_{2,q}$									
Scenario 3									
p \ q	10	20	30	40	50	60	70	80	90
10	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	6.25	12.50	18.75	25.00
70	0	0	0	0	0	12.50	25.00	37.50	50.00
80	0	0	0	0	0	18.75	37.50	56.25	75.00
90	0	0	0	0	0	25.00	50.00	75.00	100.00

3.2. Quantile mediation

We fit the following quantile regressions using the observed values to estimate the quantile-specific mediated effects (i.e., $\beta_{1,p} * \gamma_{2,q}$):
$\psi_p(M_i|A_i) = \beta_{0,p} + \beta_{1,p}\ A_i$
$\zeta_q(Y_i|A_i, M_i) = \gamma_{0,q} + \gamma_{1,q}\ A_i + \gamma_{2,q}\ M_i$.

We compare the quantile-specific mediated effects to the mean mediated effects (i.e., $\beta_{1,mean} * \gamma_{2,mean}$) estimated with a standard mean mediation analysis :
$E(M_i|A_i) = \beta_{0,mean} + \beta_{1,mean}\ A_i$
$E(Y_i|A_i, M_i) = \gamma_{0,mean} + \gamma_{1,mean}\ A_i + \gamma_{2,mean}\ M_i$.

We also compare our results to the mediated effects ($\beta_{1,mean} * \gamma_{2,q}$) estimated via Imai's approach :

$E(M_i|A_i) = \beta_{0,mean} + \beta_{1,mean}\ A_i$
$\zeta_q(Y_i|A_i, M_i) = \gamma_{0,q} + \gamma_{1,q}\ A_i + \gamma_{2,q}\ M_i.$

3.3. Results

The estimated mediated effects using our quantile-specific mediation approach corresponding to Scenarios 1, 2, and 3 are presented in Tables 1, 2, and 3. When the signal occurs only at the 90^{th} decile and above, the quantile mediation method detects a signal for the mediated effect (at the 90^{th} deciles of the mediator and outcome distributions) equal to 113.8 (see Table 1), which is fairly close to the ”true” signal (i.e., 100). However, the procedure lacks power to detect it (i.e., wide confidence [-14.3 to 122.6]). When the signal occurs at the 80^{th} decile and above, the quantile mediation method detects signals at 80^{th} and 90^{th} deciles of the mediator and outcome distributions. However, the method tends to overestimate the true signals (see Table 2), which may be due to the construction of Y_{obs} as a function of $\mathrm{M}_i^{obs} * \gamma_{2,q}$. Shifting observations between the 80^{th} and 90^{th} deciles may influence observations above the 90^{th} decile. The results for Scenario 3 are similar and can be found in Table 3.

Mediated effects comparing Scenarios 1, 2, and 3 but estimated using existing approaches (i.e., mean mediation and Imai's methods) can be found in Table 4. Both methods using mean regressions eventually detect a signal when a larger portion of the population is affected, but is unable to provide any sensible picture about heterogeneous responses based on the mediator and outcome levels. Our approach is able to detect quantile-specific signals when the mediated effects is present only at the extreme quantiles of the mediator and outcome distributions.

Estimates of the quantile mediated effects $\beta_{1,p}\gamma_{2,q}$ and their associated 95%CI$_{Bootstrap}$									
Scenario 1									
p \ q	10	20	30	40	50	60	70	80	90
10	0.1	0.0	0.0	-0.1	-0.1	0.0	0.0	-0.1	-5.8
	[-0.1; 0.8]	[-0.4; 0.4]	[-0.2; 1.0]	[-1.6; 0.2]	[-1.3; 0.2]	[-1.3; 0.3]	[-1.3; 0.2]	[-1.7; 0.1]	[-69.4; 2.0]
20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
	[-0.1; 0.1]	[-0.1; 0.1]	[-0.1; 0.1]	[-0.1; 0.1]	[-0.1; 0.2]	[-0.1; 0.2]	[-0.1; 0.2]	[-0.1; 0.2]	[-3.8; 6.3]
30	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-1.3
	[-0.1; 0.1]	[-0.1; 0.1]	[-0.1; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.1; 0.1]	[-0.1;0.1]	[-0.2;0.1]	[-6.4; 3.1]
40	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	-3.0
	[0.0; 0.1]	[-0.1;0.1]	[-0.1; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.3; 0.1]	[-7.7; 1.3]
50	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	-4.1
	[-0.1; 0.2]	[-0.1; 0.1]	[-0.1; 0.2]	[-0.2; 0.1]	[-0.3; 0.1]	[-0.3; 0.1]	[-0.2; 0.1]	[-0.3; 0.1]	[-8.5; 1.0]
60	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-2.8
	[0.0; 0.1]	[-0.1; 0.1]	[-0.1; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-7.4; 2.0]
70	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	-3.3
	[0.0; 0.2]	[-0.1; 0.1]	[-0.1; 0.2]	[-0.2; 0.1]	[-0.3; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.3; 0.1]	[-8.2; 1.7]
80	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	-3.0
	[0.0; 0.1]	[-0.1; 0.1]	[-0.1; 0.2]	[-0.3; 0.1]	[-0.3; 0.1]	[-0.3; 0.1]	[-0.2; 0.1]	[-0.3; 0.1]	[-7.8; 2.1]
90	-1.1	-0.3	-0.8	1.3	1.3	1.0	0.9	1.9	113.8
	[-3.3; 1.3]	[-1.6; 4.2]	[-2.2; 5.5]	[-2.6; 5.0]	[-8.5; 1.0]	[-7.4; 2.0]	[-8.2; 1.7]	[-7.8; 2.1]	[-14.3;122.6]

Table 1. Results of the simulation study: scenario 1 ($\beta_{1,p} = \gamma_{2,q}$=0 for all deciles p, q, except for p=$q \geq$ 90, $\beta_{1,90} = \gamma_{2,90}$=10)

Scenario 2	Estimates of the quantile mediated effects $\beta_{1,p}\gamma_{2,q}$ and their associated 95%CI$_{Bootstrap}$								
10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-1.3	-3.5
	[-0.1; 0.3]	[-0.4; 0.1]	[-0.4; 0.1]	[-0.3; 0.2]	[-0.4; 0.2]	[-0.4; 0.2]	[-0.5; 0.1]	[-5.9; 1.7]	[-92.8; 5.3]
20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.9	-2.5
	[-0.1; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.3; 0.1]	[-4.1; 2.0]	[-13.1; 5.8]
30	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.9	-2.6
	[-0.1; 0.1]	[-0.1; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2;0.1]	[-3.2;1.8]	[-9.7; 5.3]
40	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	-1.6	-4.4
	[0.0; 0.1]	[-0.2;0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.3; 0.1]	[-3.9; 0.9]	[-11.8; 3.0]
50	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	-0.2	5.4
	[-0.1; 0.1]	[-0.1; 0.1]	[-0.1; 0.1]	[-0.1; 0.1]	[-0.1; 0.1]	[-0.1; 0.1]	[-0.2; 0.1]	[-2.7; 1.5]	[-8.3; 4.8]
60	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.5	-1.5
	[-0.1; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-0.2; 0.1]	[-3.3; 1.6]	[-10.1; 6.2]
70	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	[-0.1; 0.1]	[-0.1; 0.1]	[-0.2; 0.1]	[-0.1; 0.1]	[-0.2; 0.1]	[-0.1; 0.1]	[-0.2; 0.1]	[-3.1; 2.4]	[-9.7; 7.7]
80	-0.4	0.4	0.6	0.7	0.7	0.5	1.0	27.6	**75.2**
	[-1.6; 0.6]	[-0.8; 2.0]	[-1.1; 2.7]	[-1.3; 2.4]	[-1.0; 2.4]	[-1.2; 2.5]	[-0.8; 2.8]	[-4.6; 31.3]	**[64.3; 83.3]**
90	-0.8	0.8	1.2	1.4	1.4	1.1	2.0	56.7	**154.7**
	[-69.4; 2.0]	[-3.8; 6.3]	[-6.4; 3.1]	[-7.7; 1.3]	[-2.0; 5.0]	[-2.5; 5.0]	[-1.6; 5.7]	[-9.1; 63.2]	**[138;166.3]**

Table 2. Results of the simulation study: scenario 2 ($\beta_{1,p} = \gamma_{2,q}$=0 for all deciles p, q, except for p=$q \geq 80$, $\beta_{1,80} = \gamma_{2,80}$=5 and $\beta_{1,90} = \gamma_{2,90}$=10)

Estimates of the quantile mediated effects $\beta_{1,p}\gamma_{2,q}$ and their associated 95%CI$_{Bootstrap}$									
Scenario 3									
p \ q	10	20	30	40	50	60	70	80	90
10	0.0 [-0.3; 0.3]	0.0 [-0.4; 0.5]	0.0 [-0.8; 0.4]	0.0 [-1.2; 0.3]	0.0 [-1.0; 0.4]	-0.2 [-3.8; 10.3]	1.6 [-1.3; 31.2]	9.0 [-6.3; 174.3]	9.3 [-6.5; 181.5]
20	0.0 [-0.1; 0.1]	0.0 [-0.1; 0.1]	0.0 [-0.1; 0.1]	0.0 [-0.2; 0.1]	0.0 [-0.2; 0.1]	-0.1 [-0.7; 1.7]	1.0 [-1.6; 4.1]	5.8 [-10.0; 20.6]	6.0 [-10.4; 21.4]
30	0.0 [-0.1; 0.1]	0.0 [-0.1; 0.1]	0.0 [-0.1; 0.1]	0.0 [-0.1; 0.1]	0.0 [-0.1; 0.1]	0.1 [-1.3; 0.6]	-0.6 [-3.1; 1.9]	-3.1 [-15.9; 10.2]	-3.3 [-16.4; 10.6]
40	0.0 [-0.1; 0.1]	0.0 [-0.1;0.1]	0.0 [-0.1; 0.1]	0.0 [-0.2; 0.1]	0.0 [-0.1; 0.1]	-0.1 [-0.6; 1.3]	0.8 [-1.5; 3.0]	4.5 [-8.1; 16.2]	4.7 [-8.4; 17.0]
50	0.0 [-0.1; 0.1]	0.0 [-0.1; 0.1]	0.0 [-0.1; 0.1]	0.0 [-0.2; 0.1]	0.0 [-0.1; 0.1]	-0.1 [-0.5; 1.4]	1.0 [-0.8; 3.5]	5.9 [-4.2; 17.5]	6.1 [-4.3; 18.2]
60	0.0 [-0.5; 0.5]	0.0 [-0.8; 1.0]	-0.1 [-0.9; 0.9]	-0.2 [-1.2; 0.7]	0.0 [-1.2; 0.8]	-1.4 [-2.9; 8.9]	**12.2 [8.8; 22.6]**	**68.4 [58.0; 84.4]**	**71.3 [60.6; 87.9]**
70	0.0 [-0.9;0.8]	0.0 [-1.5;1.8]	-0.2 [-1.7;1.5]	-0.4 [-2.2;1.3]	-0.1 [-2.1;1.5]	-2.7 [-5.2;16.2]	**22.7 [16.3;40.4]**	**127.9 [115.2;141.9]**	**133.2 [120.1;147.3]**
80	0.0 [-1.3;1.2]	0.0 [-2.2;2.7]	-0.3 [-2.5;2.2]	-0.7 [-3.3;1.8]	-0.1 [-3.1;2.2]	-4.0 [-7.6;23.6]	**33.6 [24.6;59.7]**	**188.9 [174.9;203.8]**	**196.8 [181.7;211.9]**
90	-0.1 [-1.7;1.6]	0.0 [-2.9;3.4]	-0.4 [-3.2;2.8]	-0.9 [-4.3;2.4]	-0.2 [-3.9;2.7]	-5.2 [-9.8;30.5]	**43.7 [9.5;77.1]**	**246.0 [53.4;263.4]**	**256.2 [55.8;273.8]**

Table 3. Results of the simulation study: scenario 3 ($\beta_{1,p} = \gamma_{2,q}$=0 for all deciles p, q, except for p=$q \geq$ 60, $\beta_{1,60} = \gamma_{2,60}$=2.5, $\beta_{1,70} = \gamma_{2,70}$=5, $\beta_{1,80} = \gamma_{2,80}$=7.5, and $\beta_{1,90} = \gamma_{2,90}$=10)

Estimates of the quantile mediated effects $\beta_{1,p} * \gamma_{2,q}$ and their associated 95%CI$_{Bootstrap}$		
Scenario 1		
Mean mediation	$\beta_{1,mean} * \gamma_{2,mean}$	0.7 [-0.6; 2.0]
Imai's method	$\beta_{1,mean} * \gamma_{2,10}$	-0.1 [-0.3; 0.1]
	$\beta_{1,mean} * \gamma_{2,20}$	0.0 [-0.4; 0.2]
	$\beta_{1,mean} * \gamma_{2,30}$	0.0 [-0.4; 0.2]
	$\beta_{1,mean} * \gamma_{2,40}$	0.1 [-0.2; 0.5]
	$\beta_{1,mean} * \gamma_{2,50}$	0.1 [-0.2; 0.5]
	$\beta_{1,mean} * \gamma_{2,60}$	0.1 [-0.3; 0.5]
	$\beta_{1,mean} * \gamma_{2,70}$	0.0 [-0.2; 0.4]
	$\beta_{1,mean} * \gamma_{2,80}$	0.1 [-0.2; 0.6]
	$\beta_{1,mean} * \gamma_{2,90}$	6.1 [-4.7; 15.6]
Scenario 2		
Mean mediation	$\beta_{1,mean} * \gamma_{2,mean}$	**2.8 [0.4; 5.6]**
Imai's method	$\beta_{1,mean} * \gamma_{2,10}$	-0.1 [-0.5; 0.2]
	$\beta_{1,mean} * \gamma_{2,20}$	0.1 [-0.2; 0.7]
	$\beta_{1,mean} * \gamma_{2,30}$	0.2 [-0.3; 0.8]
	$\beta_{1,mean} * \gamma_{2,40}$	0.1 [-0.3; 0.8]
	$\beta_{1,mean} * \gamma_{2,50}$	0.2 [-0.3; 0.9]
	$\beta_{1,mean} * \gamma_{2,60}$	0.1 [-0.3; 0.8]
	$\beta_{1,mean} * \gamma_{2,70}$	0.3 [-0.2; 0.9]
	$\beta_{1,mean} * \gamma_{2,80}$	5.7 [-0.3; 11.1]
	$\beta_{1,mean} * \gamma_{2,90}$	**19.8 [2.9; 37.6]**
Scenario 3		
Mean mediation	$\beta_{1,mean} * \gamma_{2,mean}$	**19.1 [11.8; 26.5]**
Imai's method	$\beta_{1,mean} * \gamma_{2,10}$	0.0 [-0.6; 0.6]
	$\beta_{1,mean} * \gamma_{2,20}$	0.0 [-1.0; 1.2]
	$\beta_{1,mean} * \gamma_{2,30}$	-0.2 [-1.1; 0.9]
	$\beta_{1,mean} * \gamma_{2,40}$	0.1 [-0.3; 0.8]
	$\beta_{1,mean} * \gamma_{2,50}$	-0.1 [-1.4; 0.9]
	$\beta_{1,mean} * \gamma_{2,60}$	-0.1 [-3.3; 9.4]
	$\beta_{1,mean} * \gamma_{2,70}$	**18.7 [8.8; 32.3]**
	$\beta_{1,mean} * \gamma_{2,80}$	**78.5 [49.8; 107.9]**
	$\beta_{1,mean} * \gamma_{2,90}$	**81.7 [50.0; 112.6]**

Table 4. Results of the scenarios 1 to 3 of the simulation study using existing mediation analysis methods

